UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Absorption Standard Review and Study Reviews for PMN 08-508/509

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[redacted]

I. INTRODUCTION

PMN substance 08-508, 2,3,3,3-tetrafluoro-2-(1,1,2,2,3,3,3-heptafluoropropoxy)propanoic acid (CAS No. 13252-13-6, Figure 1), is a [redacted] with a molecular weight of 330, a boiling point of [redacted] (PMN submission), an estimated water solubility of 43 mg/L, and an estimated log K_{ow} of 8.12 (SAT Report).

PMN substance 08-509, 2,3,3,3-tetrafluoro-2-(1,1,2,2,3,3,3-heptafluoropropoxy)propanoic acid ammonium salt (CAS No. 62037-80-3, Figure 1), is a solid with a molecular weight of 347, it is dispersible in water (SAT Report).

II. CONCLUSIONS

A. Absorption: Absorption of the PMN substances through the skin is expected to be poor although extent of absorption may be increased by the acidity (508) or

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[redacted]

surfactant properites (509) of the compounds. Absorption from the lung and GI tract is expected to be good.

Estimated percent absorbed:
SKIN: 6.2 ± 5.3 µg/cm²/h (human); 70 ± 5.3 µg/cm²/h (rat)
LUNG: 100%
GI TRACT: Unknown

B. Metabolism: Over short residence time no metabolism of the PMN substances is expected.

III. BASES FOR CONCLUSIONS

A. Absorption:

1. Skin: The submitter provided an *in vitro* study (see below; [redacted]) investigating the dermal penetration of PMN substance 509 through human and rat skin, results as indicated above.

2. Lung: Water-soluble compounds with molecular weights in the range of 300 to 1,400 [e.g., sucrose, MW = 342, and cyanocobalamin (Vitamin B_{12}), MW = 1,355] and with low lipid solubility are absorbed from the lung (half-life 84 to 190 min in adult rats, (Schanker and Hemberger, 1983).

3. GI Tract: When pregnant rats were dosed via oral gavage with [redacted] (dose not reported) a maximum maternal blood level of 20 µg/mL was measured at 4 hours post dosing [redacted]). Sufficient information was not available from this study to determine the extent of absorption.

B. Metabolism: The submitter provided an *in vitro* study (see below; [redacted]) investigating the metabolism of PMN substance 509 by liver microsomes. No apparent loss of parent compound was noted.

IV. REVIEW OF STUDY FOR PMN SUBSTANCE 508

A. Pharmacokinetics in rats

Groups of 3 male and 3 female rats were dosed via single oral gavage with either 10 or 30 mg/kg of PMN substance 508 (98%). Blood samples were taken before dosing and at 0.25, 0.5, 1, 2, 4, 8, 12, 24, 48, 72, 96, 120, 144, and 168 hours after dosing. In addition fat and liver samples were taken at terminal sacrifice. Samples were

analyzed for parent compound suing HPLC/MS with a level of quantitation (LOQ) of 20 ng/mL [redacted]).

Clearance times for PMN substance 508 (time for clearance of 98.4% of the compound) were calculated:

	10 mg/kg	30 mg/kg
Male	28 h	22 h
Female	8 h	4 h

All fat samples and female rat liver samples were below the LOQ. Tissue (liver)/plasma ratio for male rats: 10 mg/kg = 0.64; 30 mg/kg = 0.71.

V. REVIEW OF STUDIES FOR PMN SUBSTANCE 509

A. Pharmacokinetics in Rats

Groups of 3 male and 3 female rats were dosed via single oral gavage with either 10 or 30 mg/kg of PMN substance 509 (84.5%). Blood samples were taken before dosing and at 0.25, 0.5, 1, 2, 4, 8, 12, 24, 48, 72, 96, 120, 144, and 168 hours after dosing. In addition fat and liver samples were taken at terminal sacrifice. Samples were analyzed for parent compound suing HPLC/MS with a level of quantitation (LOQ) of 20 ng/mL [redacted]).

Clearance times for PMN substance 509 (time for clearance of 98.4% of the compound) were calculated:

	10 mg/kg	30 mg/kg
Male	12 h	22 h
Female	4 h	8 h

All fat samples and female rat plasma samples were below the LOQ. Tissue (liver)/plasma ratio for male rats: 10 mg/kg = 2.2; 30 mg/kg = 0.8.

B. *In Vitro* Metabolism

PMN substance 509 was incubated for 5, 15, 30, 45, 60, 90, or 120 minutes at 37°C with rat liver microsomes. Heat-inactivated microsomes were used as control.

After 2 hours there was no apparent loss of parent compound was noted.

[redacted]

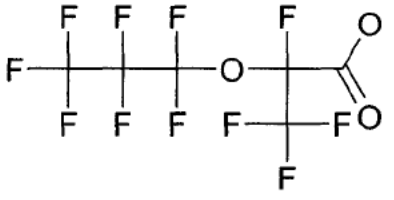
C. *In Vitro* Dermal Penetration

Samples of human and rat skin were dermatomed to uniform thickness of approximately 450 µm and mounted in static diffusion cells. Receptor fluid was saline. Cells were maintained at 32°C. An aqueous solution (124 mg/mL) of PMN substance 509 (86%) was added to the donor chamber and samples of the receptor fluid were removed at 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 12, and 24 hours. These samples were analyzed for parent compound using HPLC/MS. A permeability coefficient (K_p in cm/h) was calculated by dividing the penetration rate at steady state (µg/cm²/h) by the concentration of the applied chemical (µg/cm³).

Summary of Kinetic Parameters for 509			
		Mean	SD
Human	Lag Time (h)	1.73	1.01
	Penetration rate (µg/cm²/h)	6.18	5.27
	K_p (cm/h)	5.02 E-05	4.3 E-05
Rat	Lag Time (h)	0.82	0.77
	Penetration rate (µg/cm²/h)	70.3	5.27
	K_p (cm/h)	5.71 E-04	4.3 E-05

[redacted]

PMN Substance 08-508



PMN Substance 08-509

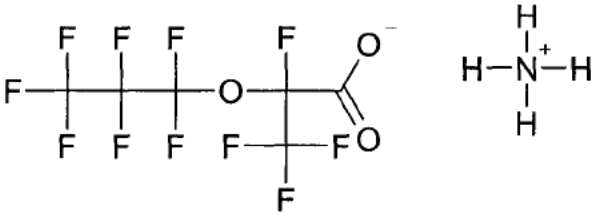


Figure 1. Structures of PMN Substances 08-508/509

[redacted]

REFERENCES

[redacted] 1982 (March 16 *et seq.*).

[redacted] 2008 (Feb. 27). Determination of a permeability coefficient (K_p) for H-28308 [PMN substance 509] using human and rat skin mounted in an in vitro static diffusion cell. Conducted for DuPont. Submitted in P08-508/509.

[redacted] 2008a (Feb. 13). Biopersistence and pharmacokinetic screen in the Rat [for PMN substance 508]. Performed by DuPont Haskell Global Center for Health & Environmental Sciences for DuPont. [redacted] Submitted in P08-508/509.

[redacted] 2008b (Feb. 13). Biopersistence and pharmacokinetic screen in the Rat [for PMN substance 509]. Performed by DuPont Haskell Global Center for Health & Environmental Sciences for DuPont. [redacted] Submitted in P08-508/509.

[redacted]). 2007 (June 12). In Vitro Rat Hepatocyte Screen [for PMN substance 509]. Performed for DuPont. [redacted] Submitted in P08-508/509.

Schanker LS, Hemberger JA. 1983. Relation between molecular weight and pulmonary absorption rate of lipid-insoluble compounds in neonatal and adult rats. Biochem. Pharmacol. 32:2599-2601.

[redacted]